

Risk for Significant Kidney Function Decline After Acute Kidney Injury in Adults With Hematologic Malignancy



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Introduction: Acute kidney injury (AKI) affects 30% of adults hospitalized with hematologic malignancy. Little is known about the long-term impact on kidney outcomes in this population despite the close relationship between kidney function and malignancy treatment eligibility. The purpose of this population-based cohort study was to determine the effect of AKI on kidney function in the year following a new diagnosis of acute leukemia or lymphoma.

Methods: Participants were adults hospitalized within 3 weeks of malignancy diagnosis. Baseline kidney function was determined and AKI diagnosed using standardized criteria. Cox proportional hazard modeling examined the relationship between AKI and a $\geq 30\%$ decline in estimated glomerular filtration rate (eGFR) from baseline in the 1 year following hospitalization as the primary endpoint.

Results: AKI occurred in 33% of 1064 participants, with 70% of episodes occurring within 48 hours of hospitalization, and significantly increased risk for a $\geq 30\%$ decline in eGFR (hazard ratio [HR] 2.7, 95% confidence interval [CI] 2.2–3.5) and incident chronic kidney disease (HR 2.2, 95% CI 1.7–2.8). AKI remained a significant predictor of eGFR decline in subgroup and multivariable analyses (adjusted HR 1.9, 95% CI 1.4–2.7). A $\geq 30\%$ decline in eGFR increased the risk for death within 1 year in participants with AKI (HR 2.1, 95% CI 1.3–3.3).

Conclusion: Results aid in identifying individuals at highest risk for poor outcomes and highlight the need for research involving interventions that preserve kidney function from the time of initial hospitalization with a hematologic malignancy into the postdischarge period.

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KEYWORDS: cancer; kidney function; kidney injury; leukemia; lymphoma; outcomes

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AKI is a major barrier to positive health outcomes and is known to affect at least 30% of adults hospitalized with newly diagnosed hematologic malignancies, often as a result of hypoperfusion, tumor lysis syndrome, and chemotherapy-induced nephrotoxicity.^{1–4} Short-term consequences of AKI in this setting include increased hospital mortality and a tripling of lengths of stay and cost.^{2,5,6} Any resultant permanent loss of kidney function may jeopardize

eligibility for optimal cancer treatments and, ultimately, survival.

Less is known about the long-term impact of AKI in patients with hematologic malignancy, despite a growing interest in post-hospital consequences for AKI survivors. Individuals with hematologic malignancy comprise a small portion of study samples in large population studies and the degree to which these findings are generalizable in this unique sub-population is unknown. Conversely, small sample sizes and limited durations of follow-up from published studies of patients with AKI and hematologic malignancy make it difficult to appreciate the long-term effects on kidney function and health outcomes. A malignancy diagnosis (of any type) was associated with a 1.9-fold risk of rehospitalization with recurrent AKI in a cohort of

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adults surviving an initial AKI episode and not discharged on dialysis.⁷ Results from a study of patients admitted to the intensive care unit with select, high-grade hematologic malignancies showed that those with AKI were 0.58 times as likely to be alive in complete remission at 6 months, and chemotherapy modifications were required in 15% of patients as a result of the AKI episode.³ Critically ill patients included in this study were those with only the most aggressive hematologic malignancies and previously normal kidney function. Although existing findings are notable, the current literature contains key knowledge gaps. It is essential to further explore the relationship between AKI and long-term kidney outcomes in a more representative sample of hematologic malignancy diagnoses, in patients with pre-existing comorbidities, and in those outside of the intensive care unit. This will allow for identification of individuals at high risk for poor outcomes and inform interventions to protect and preserve kidney function, a key determinant of eligibility for preferred chemotherapy, hematopoietic cell transplantation, novel immunotherapy, and clinical trials. The purpose of this investigation was to determine the effect of AKI on kidney function in the year following a diagnosis of acute leukemia or lymphoma. Recognizing the unique differences between malignancies and treatment approaches, participants with acute leukemia and lymphoma were evaluated in aggregate as well as individually.

METHODS

Study Design and Sample

A population-based cohort study was performed from 2005 to 2017 using the Rochester Epidemiology Project, a medical records linkage system that unifies records from multiple medical care providers in Olmsted County, Minnesota and the surrounding 27 counties. The Rochester Epidemiology Project includes demographic data and comprehensive information related to diagnoses, hospital admissions and outpatient follow-up care.⁸ Residents have similar age- and sex-specific mortality rates to those found in Minnesota and the United States.⁹ We identified adults (≥ 18 years of age) with newly diagnosed or relapsed acute leukemia or lymphoma who were hospitalized within 3 weeks of the diagnosis. Diagnoses were identified using *International Classification of Diseases, Ninth and Tenth Revision* diagnosis codes recorded within 60 days of pathology or hematopathology studies ([Supplementary Table S1](#)). The requirement of corresponding pathology studies was implemented in order to enhance the validity of the diagnosis codes by decreasing the

likelihood of misclassification bias. Participants were included only once, at the time of the index hospitalization within this time frame. Those diagnosed in 2005 were evaluated for a malignancy diagnosis assigned in the preceding year to ensure no prevalent cases were included. Relapsed disease was identified if a malignancy diagnosis code that matched the code assigned at cohort entry was recorded more than 1 year before study inclusion. Those with pre-existing end-stage kidney disease requiring dialysis were excluded.

Identification of AKI

Data were electronically abstracted from the Rochester Epidemiology Project Database. Pertinent demographic data included age at diagnosis, anthropometrics, hematologic disease subtype, and a history of cardiovascular or chronic kidney disease, diabetes, or hypertension. Comorbidities were identified using *International Classification of Diseases, Ninth and Tenth Revision*, diagnosis codes. Diagnosis with one of these comorbidities required 2 codes separated by at least 30 days within 3 years of hospitalization in order to reduce the potential for misclassification bias. A baseline serum creatinine (SCr) was established for each member of the cohort using the median outpatient SCr values from the period of 6 months up to 7 days prior to hospitalization or, if unavailable, estimated using the MDRD formula.¹⁰ This SCr was also used to determine baseline eGFR prior to study entry, calculated using the Chronic Kidney Disease Epidemiology Collaborative equation. Routine laboratory data collected from the hospital encounter included SCr measurements, which were used to identify and stage AKI per the KDIGO criterion.¹¹ AKI was classified as community- or hospital-acquired based on time of onset (within 48 hours of hospitalization for community-acquired AKI, > 48 hours for hospital-acquired AKI).¹² Referent participants were free of any stage AKI throughout the duration of their hospitalization.

Outcome Assessment

The primary outcome of interest was a $\geq 30\%$ decline in eGFR from baseline in the 1 year following hospitalization. The threshold of $\geq 30\%$ decline was selected because it has been strongly associated with increased risk for end-stage kidney disease and all-cause mortality in the general population.¹³ As CKD requires persistent kidney dysfunction for a minimum of 90 days following an episode of AKI,¹¹ the outcome was assessed between 90 and 365 days after the last day of hospitalization using serially collected SCr data to calculate eGFR. A minimum of 1 SCr value, obtained in the outpatient setting, was required for inclusion in the

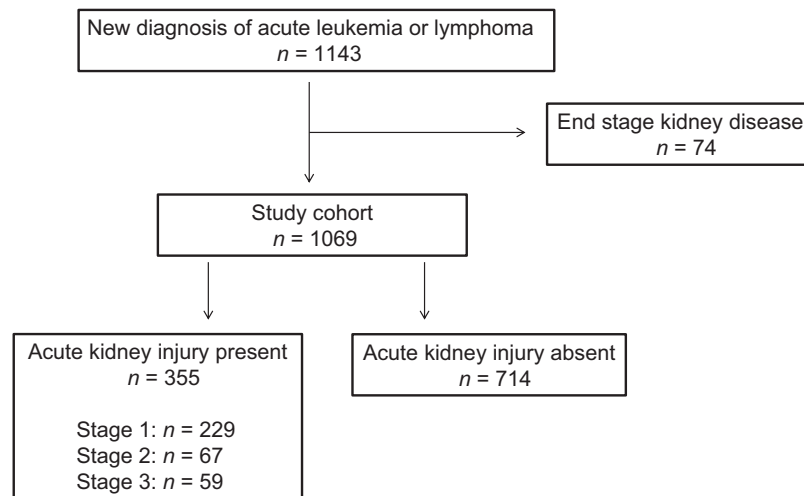


Figure 1. Flowchart for included participants.

analysis. Participants with a baseline eGFR ≥ 60 ml/min per 1.73 m^2 were considered to have normal baseline kidney function and were evaluated for new CKD stage 3 or higher, defined as eGFR < 60 ml/min per 1.73 m^2 , during the follow-up period.¹¹ Review of medical records for follow-up was conducted for up to 12 months or until death or loss of follow-up, whichever occurred first.

Statistical Analysis

Descriptive statistics were used to report demographics for the entire cohort and for the groups with and without AKI. Univariate Cox proportional hazard modeling estimated the HR for a $\geq 30\%$ decline in eGFR from baseline in the aggregate cohort and in subgroups based on malignancy type (acute leukemia or lymphoma). We also compared the HR for a $\geq 30\%$ decline in eGFR from baseline according to maximum AKI stage. Multivariable Cox proportional hazard modeling included the following clinically relevant variables: age, sex, year of diagnosis, eGFR at baseline and hospital dismissal, malignancy subtype (including acute myeloid leukemia, acute lymphoblastic leukemia, other leukemia, non-Hodgkin lymphoma, and other lymphoma), relapsed disease, comorbidities (including cardiovascular or chronic kidney disease, diabetes, and hypertension), and hospital readmission, hematopoietic cell transplant, or subsequent AKI episode during the follow-up period. The model was checked for non-proportionality to ensure no violations were found. Cumulative incidence curves, adjusted for competing risk of death, described the time to a $\geq 30\%$ decline in eGFR from baseline in those with and without AKI and by AKI stage. To explore the association between experiencing an episode of AKI and/or a $\geq 30\%$ decline in eGFR from baseline and survival, Cox proportional hazard modeling was performed. This

modeling used a 4-level categorical variable for the combinations of having an AKI and/or $\geq 30\%$ decline in eGFR as a time-dependent covariate for the prediction of survival. All HRs are reported with their corresponding 95% CIs using a 2-tailed alpha level of < 0.05 to indicate statistical significance.

RESULTS

Participants

There were 1143 individuals with newly diagnosed or relapsed acute leukemia or lymphoma during the study time frame, of which 1069 were included (Figure 1) and are described in Table 1. Relapsed disease was present in only 33 (3%) cohort participants. Demographics and baseline characteristics, including baseline kidney function, were similar between those with acute leukemia and those with lymphoma (Supplementary Tables S2 and S3).

Of the 355 participants who experienced AKI, 249 episodes (70%) were community-acquired and 106 (30%) were hospital-acquired. Of the 59 participants with AKI stage 3, 33 (56%) required dialysis during the hospitalization and 17 (29%) required dialysis at least once within 90 days after hospitalization. AKI occurred in 190 participants (43%) with acute leukemia and 165 (26%) with lymphoma (Table 2).

Outcomes

Of the 1069 participants, 755 (71%) had adequate follow-up for assessment of the primary outcome of a $\geq 30\%$ decline in eGFR. Outcome assessment was possible in 64% of participants with AKI and 74% of referent participants. The primary identifiable reason for insufficient follow-up was death ($n = 239$). Loss of follow-up occurred in 35% and 25% of participants with acute leukemia and lymphoma, respectively, with death as the reason in 84% of the individuals with

Table 1. Participant characteristics

Characteristic	Total cohort (N = 1069)	AKI (n = 355)	No AKI (n = 714)
Age, yr	67 (54–76)	67 (54–76)	66 (55–78)
Male sex, n (%)	624 (58)	242 (68)	382 (54)
White race, n (%)	1002 (94)	327 (92)	675 (95)
Body mass index	28 (24–33)	28 (25–34)	27 (24–32)
Malignancy subtype, n (%)			
Acute leukemia	440 (41)	190 (54)	250 (35)
Lymphoma	629 (59)	165 (46)	464 (65)
Cardiovascular disease, n (%)	183 (17)	65 (18)	118 (17)
Diabetes, n (%)	190 (17)	74 (21)	116 (16)
Hypertension, n (%)	367 (34)	126 (36)	241 (34)
Chronic kidney disease, n (%)	82 (8)	31 (9)	51 (7)
Baseline SCr, mg/dL	0.9 (0.8–1.1)	0.8 (0.7–1)	0.9 (0.8–1.1)
Baseline eGFR, ml/min per 1.73 m ²	80 (63–95)	84 (63–101)	78 (63–94)

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; SCr, serum creatinine. Continuous data are reported as median (interquartile range).

acute leukemia and 68% of the individuals with lymphoma. The median (IQR) number of follow-up SCr measurements between 90 and 365 days following hospitalization was 22 (6–51) in participants with AKI and 11 (5–35) in referent participants without AKI during index hospitalization.

Cumulative incidence of a $\geq 30\%$ decline in eGFR from baseline at 1 year was 68% (95% CI 57–76) for those with any stage AKI and 39% (95% CI 32–45) for referent participants without AKI during the index hospitalization, with a corresponding HR of 2.7 (95% CI 2.2–3.5; $P < 0.001$) in univariate analysis. Subgroup analyses by malignancy subtype and AKI stage revealed similar results (Table 3). Figure 2 depicts the time to a $\geq 30\%$ decline in eGFR, adjusted for the competing risk of death. Table 4 describes the relationship between a $\geq 30\%$ decline in eGFR and risk for death within 1 year.

The relationship between AKI during hospitalization and a $\geq 30\%$ decline in eGFR from baseline remained significant in multivariable analysis, with an HR of 1.9 (95% CI 1.4–2.7; $P = 0.001$) (Figure 3). Other factors that were associated with a $\geq 30\%$ decline in eGFR included age, eGFR at baseline and at hospital dismissal, an AKI episode or hematopoietic cell transplant during the follow-up period after index hospitalization, and select malignancy diagnoses.

Among all participants with normal baseline kidney function ($n = 620$), the frequency of incident CKD based on outpatient eGFR at 1 year was 51% in those with any stage AKI and 32% in referent participants free from AKI during the index hospitalization (HR 2.2, 95% CI 1.7–2.8; $P < 0.001$). In those with acute leukemia, 69 of 115 participants (60%) with AKI developed incident CKD, compared with 77 of 149

Table 2. AKI characteristics by malignancy subtype

	Acute leukemia (n = 190)	Lymphoma (n = 165)
AKI stage, n (%)		
Stage 1	130 (68)	99 (60)
Stage 2	34 (18)	33 (20)
Stage 3	26 (14)	33 (20)
Dialysis during hospitalization, n (%)	16 (8)	17 (10)
eGFR at hospital dismissal, ml/min per 1.73 m ²	84 (55–101)	81 (57–98)

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate. Continuous data are reported as median (interquartile range).

participants (52%) without AKI during index hospitalization (HR 1.5, 95% CI 1.1–2.1; $P = 0.009$). In those with lymphoma, 28 of 73 participants (38%) with AKI developed incident CKD, compared with 63 of 282 participants (22%) without AKI during index hospitalization (HR 2.1, 95% CI 1.3–3.3; $P = 0.001$).

DISCUSSION

AKI affects approximately 1 of every 3 individuals hospitalized with newly diagnosed or relapsed acute leukemia or lymphoma. Though the bulk of participants experienced stage 1 AKI, 35% of AKI episodes were stage 2 or 3 severity. These rates of AKI are higher than those reported in the general population.¹⁴ Frequency of AKI appeared higher in the subgroup with acute leukemia (45%–50% of those with acute myeloid or lymphoblastic leukemia) compared to the patients with lymphoma. This is possibly due to longer hospitalization and duration of neutropenia, higher infection rates, or increased exposure to nephrotoxins such as antibiotics in patients with leukemia.

The general population of AKI survivors is at increased risk for hospital readmission, cardiovascular events, CKD, and death,^{7,15–18} but it is unclear how well these data extrapolate to patients with a diagnosis of a hematologic malignancy.^{16,18} Our data showed that in a group of patients with new acute leukemia or lymphoma, an episode of AKI was associated with a 1.9-fold higher risk for significant eGFR loss and increased the risk for incident CKD among those with normal kidney function at baseline. In the overall cohort, risk for eGFR loss remained constant regardless of the stage of AKI. Although stage 2 and 3 AKI have been linked to higher risk for end-stage kidney disease and death relative to stage 1 AKI, other studies have demonstrated that the risk for outcomes such as recurrent AKI or CKD was not significantly affected by AKI stage.^{7,19} These findings underscore the potential significance of even small changes in kidney function. In the present study, incident CKD among patients with a new hematologic malignancy occurred at higher rates than in all-comers by 1 year (50% vs. 30%).^{12,20}

Table 3. Risk of a $\geq 30\%$ decline in eGFR from baseline within 1 year in univariate analysis

	All patients		Acute leukemia		Lymphoma	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AKI	2.7 (2.2–3.5)	< 0.001	1.9 (1.4–2.6)	< 0.001	2.9 (2.0–4.3)	< 0.001
AKI stage						
No AKI	Reference		Reference		Reference	
Stage 1	2.7 (2.1–3.5)	< 0.001	1.7 (1.3–2.5)	0.001	3.2 (2.1–4.8)	< 0.001
Stage 2 or 3	2.8 (2.0–4.0)	< 0.001	2.5 (1.6–3.9)	< 0.001	2.5 (1.4–4.4)	0.002

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

This is consistent with population data indicating CKD is more prevalent in those with malignancy relative to the general population,²¹ possibly because of higher frequency of acute illness and hospitalization or exposure to nephrotoxic chemotherapy.

An increase in comorbidity burden such as with new CKD is especially consequential for patients with cancer and has implications for costs, care decisions, and quality of life.^{22–24} Transplant programs and clinical trials for novel immunotherapy or chemotherapeutics often deny entry to patients with an SCr level > 1.5 mg/dL or an eGFR < 60 mL/min per 1.73 m². Preferential regimens for leukemia and lymphoma often include renally eliminated and nephrotoxic agents such as methotrexate, cyclophosphamide, and cytarabine. Development of long-term kidney dysfunction may result in these drugs being omitted from treatment programs, doses being reduced, or second- or third-line regimens being selected, all of which could adversely affect the efficacy of cancer treatment.³ Our analysis showed that the risk for death was significantly increased in those participants with a decline in eGFR $\geq 30\%$ from baseline within 1 year of diagnosis. The association was strongest among those who did not experience AKI at the outset of diagnosis (the primary variable of interest in our study), but subsequently

experienced a $\geq 30\%$ decline in eGFR from baseline. This may have been the result of AKI that occurred later during the malignancy disease course, which is not uncommon.²⁵ Our multivariable analyses also revealed a significant association between AKI episodes occurring after the index hospitalization and a $\geq 30\%$ decline in eGFR from baseline. Taken together, these findings may indicate that AKI that occurs later during a patient's treatment course has a greater effect on outcomes, for the reasons stated above. These data, as well as our primary findings of a doubling of risk for significant eGFR loss and CKD in a short, 1-year time frame, highlight the overall impact of AKI and the need for interventions that preserve kidney function from the outset of hematologic malignancy diagnosis.

Despite observing a higher proportion of patients with leukemia affected by AKI relative to those with lymphoma, the relationship between AKI and a $\geq 30\%$ decline in eGFR from baseline was stronger in the subgroup with lymphoma. This may be due to increased exposure to nephrotoxic chemotherapy (e.g., methotrexate) in the lymphoma subgroup as part of the recommended standard-of-care treatment regimens during the study time period.^{26–28} Experiencing AKI at the outset of a lymphoma diagnosis may reduce renal reserve, making individuals more susceptible to

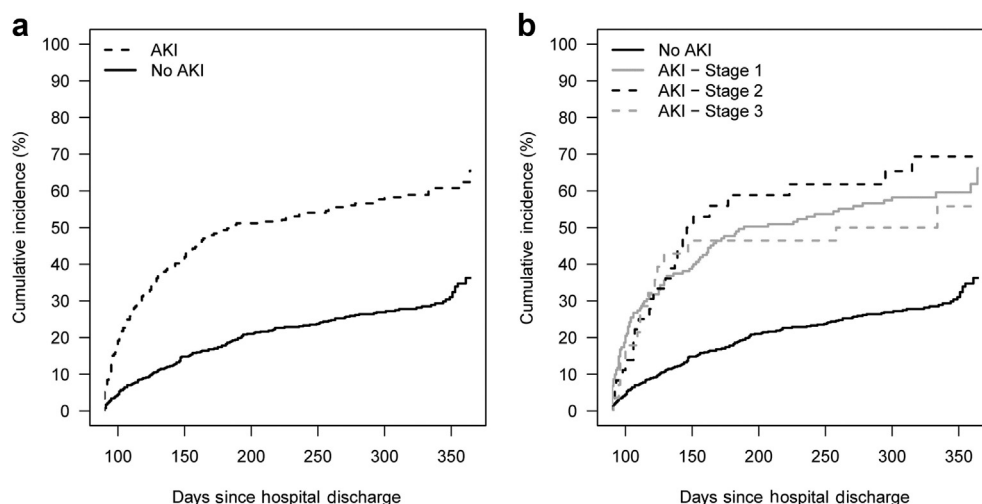


Figure 2. Time to a $\geq 30\%$ decline in eGFR from baseline in (a) the overall cohort ($P < 0.001$) and (b) by AKI stage ($P < 0.001$), adjusted for competing risk of death. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

Table 4. Relationship between a $\geq 30\%$ decline in eGFR and risk for death within 1 year

	Overall		Acute leukemia		Lymphoma	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Neither AKI nor 30% decline	Reference		Reference		Reference	
30% decline, no AKI	4.3 (2.9–6.4)	< 0.001	2.8 (1.5–5.2)	0.002	5.9 (3.5–10.0)	< 0.001
AKI, no 30% decline	1.1 (0.7–1.9)	0.71	1.0 (0.5–2.2)	0.99	1.1 (0.5–2.2)	0.86
AKI and 30% decline	2.1 (1.3–3.3)	0.002	1.4 (0.7–2.8)	0.32	2.9 (1.5–5.7)	0.002

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

permanent eGFR loss with successive exposure to nephrotoxins.^{29,30} It is also possible the lymphoma subgroup experienced subsequent episodes of AKI (after the index hospitalization) more frequently than the group with acute leukemia. Despite these differences between the subgroups, the relationship between AKI and eGFR loss and incident CKD remained significant in all analyses.

The majority of AKI episodes were evident within the first 48 hours of hospitalization. This important finding is consistent with our prior research but previously unrecognized in published literature.¹ In such cases of community-acquired AKI, kidney damage likely began early in the course of illness or perhaps preceded hospitalization.¹² This may jeopardize individuals' candidacy for first-line therapies and aggressive malignancy treatment from the outset of diagnosis.^{3,22} Higher baseline eGFR was also independently associated with significant eGFR loss. It may be that individuals with preserved eGFR more commonly undergo aggressive treatment and subsequently endure multiple kidney function insults. The pattern of AKI presentation and patients affected underscore the importance of efforts aimed at facilitating recovery from AKI, regardless of baseline kidney function, in addition to usual preventative measures. More research is needed to understand the patterns of recovery from

AKI in this population. In our multivariable model, lower eGFR at hospital dismissal was independently associated with sustained loss of eGFR. This finding has also been reported elsewhere^{16,18,31,32} and suggests that patients with AKI in whom kidney function does not recover by hospital dismissal represent an extremely high-risk population. Interventions such as careful medication reconciliation, purposeful kidney function monitoring during transitions of care, and patient education may be key to preventing comorbidity and optimizing malignancy outcomes.

This study has several limitations to consider. The potential for prevalence-incidence bias was addressed by including participants at the time the first malignancy diagnosis code was documented during the study time frame. We also evaluated those included during 2005 for a malignancy diagnosis assigned in the preceding year. It is possible that some individuals may have migrated into the population cohort with pre-existing malignancies and thus their first malignancy diagnosis codes represent prevalent cases. Additionally, sample selection was limited by the sensitivity of diagnosis codes for acute leukemia and lymphoma. We addressed this through combination of relevant codes with hematopathology data to enhance validity and decrease misclassification. Results may not be generalizable to those not requiring hospitalization or

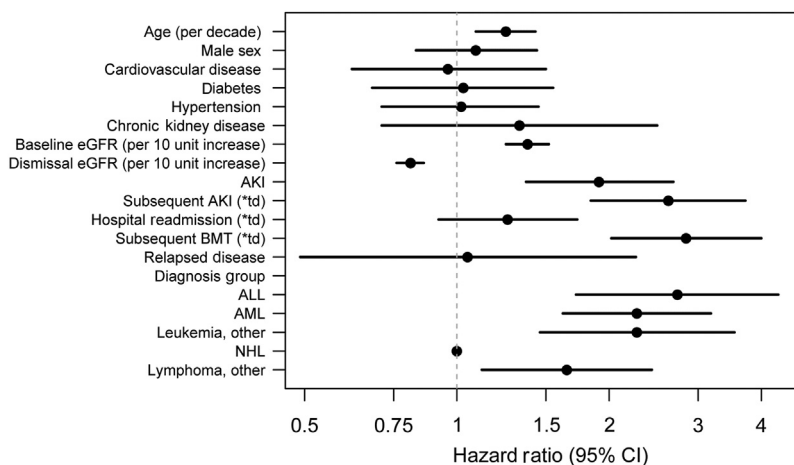


Figure 3. Risk of a $\geq 30\%$ decline in eGFR from baseline within 1 year given acute kidney injury during hospitalization in multivariable analysis. AKI, acute kidney injury; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplant; CI, confidence interval; eGFR, estimated glomerular filtration rate; HCT, hematopoietic cell transplant; NHL, non-Hodgkin lymphoma; *td, time-dependent variable.

experiencing AKI within 3 weeks of diagnosis, as such individuals may differ in overall health and complication rates from the present cohort. Prevalence of CKD at baseline appeared low in the cohort. This may be due to overestimation of eGFR in those without available baseline SCr data, poor sensitivity of CKD identifiers, or an indication of low comorbidity in individuals with a new malignancy diagnosis. This study was likely underpowered to assess how pre-existing CKD may affect the relationship between AKI and subsequent eGFR decline. Measurement bias may have resulted from different rates of follow-up assessments between individuals with and without AKI. Though the number of participants lost to follow-up was similar between groups, those with AKI were monitored more frequently. Additional effect modifiers or confounders, such as malignancy-specific characteristics or medication exposures, may exist that were not captured in this investigation, despite a robust multivariable analysis.

This large population-based cohort study is among the first to explore the relationship between AKI and kidney function outcomes in patients with newly diagnosed acute leukemia or lymphoma. Kidney function is an important determinant of eligibility for preferred chemotherapy, hematopoietic cell transplantation, and clinical trials and thus its preservation plays a vital role in optimizing malignancy outcomes. These data demonstrate that AKI at the time of new diagnosis or relapse of acute leukemia or lymphoma was associated with an increased risk for significant decline in kidney function and incident CKD in the following year. A $\geq 30\%$ decline in eGFR from baseline increased the risk for death in those with and without AKI. Results help to identify individuals at high risk for poor outcomes who stand to benefit most from action to protect and preserve kidney function. Further research is needed to determine interventions that may mitigate deleterious consequences of AKI in this unique subset of patients.

DISCLOSURE

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SUPPLEMENTAL MATERIAL

Supplementary File (PDF)

Table S1. Diagnosis codes utilized to assess for hematologic malignancy.

Table S2. Characteristics of participants with acute leukemia.

Table S3. Characteristics of participants with lymphoma.

STROBE checklist.

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